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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,371	12/08/2006	Stefan Russwurm	3535.022	7019

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PATENT CENTRAL LLC
Stephan A. Pendorf
1401 Hollywood Boulevard
Hollywood, FL 33020

EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	PAPER NUMBER
1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,371	RUSSWURM ET AL.	
	Examiner	Art Unit	
	STEPHEN KAPUSHOC	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *26 and 28-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :02/17/2010; 12/14/2009; 05/30/2009; 05/05/2009; 07/18/2007; 03/08/2007; 12/04/2006; 11/09/2008.

DETAILED ACTION

Claims 1-32 are pending.
Claims 26 and 28-32 are withdrawn from examination as detailed below.
Claims 1-25 and 27 are examined on the merits.

Election/Restrictions

1. Applicant's election with traverse of the invention of Group I, and the particular subcombination of RNAs of SEQ ID NO: 1-7, 9, 10, 78, 79, 81 and 87, in the reply filed on 11/09/2009 is acknowledged. The traversal is on the ground(s) that (p.8 of Remarks of 11/09/2009) all claims are drawn to inventions requiring the common technical feature of analysis of a body fluid. This is not found persuasive because upon inspection of the claims of the non-elected inventions (i.e. claims 26, 28, and 29-32), the non-elected groups do not in fact require analysis of a body fluid, as required by claim 1 of the elected group.

The requirement is still deemed proper and is therefore made FINAL.

Claims 26 and 28-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/09/2009.

It is noted that no claim is allowed in this Office Action, where claim 10 encompasses non-elected subcombinations of genes. Prior to the allowance of claims that recited non-elected material, any non0elected material that has not been rejoined with the elected subcombination will be required to be removed from the claim.

Information Disclosure Statement

2. The IDS of 02/17/2010 has been considered. Please note that the reference cited as “Office Action in corresponding chinese application procedure" has been lined through as this reference is not a proper citation for an IDS, and no reference has been provided by Applicants. As such this reference has not been considered.

Objection to the Specification

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See for example paras. [0039], [0068], [0081], reference number 24 on page 25. Applicants shall inspect the entirety of the specification to ensure that all instances of browser executable code are removed from the specification. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

4. Claim 1 is objected to because of the following informalities: Part e. of claim 1 recites ‘sample A’, where the phrase ‘sample RNA' is likely intended. Appropriate correction is required.

Claim Rejections – Claim 27 ‘Use’ claim

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 27 provides for the use of RNA, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 27 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

9. Claims 1-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-25 are unclear over recitation of the phrase 'differentiation between systemic inflammatory non-infections conditions (SIRS) and systemic inflammatory infectious conditions (sepsis)', as recited in the preamble of claim 1, where it is unclear if

the parenthetical terms are required limitations or merely examples of conditions. The phrase is further made unclear where recited conditions encompass diagnoses other that the recited parenthetical expressions. The claims may be made clearer if amended to recite particular conditions as consistent with the teachings of the specification, for example 'differentiation between non-septic systemic inflammatory response syndrome (SIRS) and sepsis'.

Claims 1-25 are unclear over recitation of the phrase 'the marker signals', as recited in parts e. and f. of claim 1, because there is not a proper antecedent basis for any 'marker signals' in the claim.

Claims 2 and 3 are unclear over recitation of the phrase 'the marker signal', as recited in claim 2, because there is not a proper antecedent basis for any 'marker signal' in the claim.

Claim 3 is unclear over recitation of the phrase 'unchanged gene from the sample', as recited in claim 3, because there is not a proper antecedent basis for any 'unchanged gene' in the claim.

Claim 6 is unclear over recitation of the phrase 'the clinical treatment', as recited in claim 6, because there is not a proper antecedent basis for any 'clinical treatment' in the claim.

Claim 8 is unclear over recitation of the phrase 'are in certain cases subject to lysis', as recited in claim 8, because it is unclear if the claimed method is in fact requiring some lysis, or what conditions are needed to require lysis in the claimed method.

Claims 20 and 21 are unclear over recitation of the phrase 'the sample-RNA and the control-RNA and/or enzymatic or chemical derivatives', as recited in claims 20 and 21, because there is not a proper antecedent basis for any 'enzymatic or chemical derivatives' in the claims. The claims may be made clearer in this regard if the unclear phrase is amended to recite 'the sample-RNA and the control-RNA and/or enzymatic or chemical derivatives of the sample-RNA and the control-RNA'.

Claim 22 is unclear over recitation of the phrase 'the immobilized or non-immobilized samples', as recited in claim 22, because there is not a proper antecedent basis for any 'immobilized or non-immobilized samples' in the claim.

Claim 23 is unclear over recitation of the phrase 'the DNA sample', as recited in claim 23, because there is not a proper antecedent basis for any 'DNA sample' in the claim.

Claims 24 and 25 is unclear over recitation of the phrase 'the individual DNA molecules', as recited in claims 24 and 25, because there is not a proper antecedent basis for any 'individual DNA molecules' in the claims.

Claims 24 and 25 is unclear over recitation of the phrase 'the carrier materials', as recited in claims 24 and 25, because there is not a proper antecedent basis for any 'carrier materials' in the claims.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for differentiating non-septic systemic inflammatory response syndrome (SIRS) from sepsis in a human subject, said method comprising:

a. measuring the abundance of a plurality of mRNAs in a blood sample from said human subject; and

b. comparing the abundance of the plurality of mRNAs in the blood sample from said human subject to the abundance of the plurality of mRNAs in blood samples from a control population of human subjects with non-septic SIRS;

wherein the plurality of mRNAs comprises:

(i) mRNA, expressed from the MAGED1 gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 1;

(ii) mRNA, expressed from the H1F2 gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 2;

(iii) mRNA, expressed from the DEFA4 gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 3;

(iv) mRNA, expressed from the SLC2A1 gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 4;

(v) mRNA, expressed from the IHPK1 gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 5;

(vi) mRNA, expressed from the IGLL1 gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 6;

(vii) mRNA, expressed from the FLJ12085 gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 7;

(viii) mRNA, expressed from the CA1 gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 9;

(ix) mRNA, expressed from the ZAP70 gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 10;

(x) mRNA, expressed from the IGHM gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 78;

(xi) mRNA, expressed from the KIAA0481 gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 79;

(xii) mRNA, expressed from the IGKV1D-12 gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 81; and

(xiii) mRNA, expressed from the KLF1 gene, comprising at least 20 contiguous nucleotides of SEQ ID NO: 87;

> wherein an increased likelihood of the presence of sepsis in said human subject is determined when the abundance of the plurality of mRNAs in the blood sample from said human subject is statistically significantly greater than abundance of the plurality of mRNAs in blood samples from a control population of human subjects with non-septic SIRS.

does not reasonably provide enablement for the methods as claimed which broadly encompass diagnostic methods in any mammal, sample RNA from any body fluid, and generically require any gene as having an activity for distinguishing SIRS and sepsis and encompasses gene fragments as small as 5 nucleotides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The rejected claims are drawn to methods for differentiating systemic inflammatory non-infections conditions and systemic inflammatory infectious conditions comprising comparing a sample RNA to a control RNA.

The claims encompass differentiating conditions in any subject mammal, including non-human subjects.

The claims encompass analysis sample RNA from any body fluid source (e.g. blood, bodily excretions.

The claims generically encompass any gene that has an activity “for distinguishing between SIRS and sepsis” and any fragments of genes.

The claims encompass any detected difference (e.g. any amount of compared over expression or under expression) between a sample RNA and any control RNA.

Direction provided by the specification and working example

The instant specification teaches an example wherein gene expression is measured in post-operative subjects with systemic inflammation, and the same subjects at a later time wherein the systemic inflammation is caused by sepsis. As relevant to the Election, the instant specification teaches a statistically significant increase in the expression of mRNAs of comprised of SEQ ID NO: 1-7, 9, 10 78, 79, 81 and 87 in blood of the subjects after they have sepsis as compared to the same subjects with pre-septic SIRS.

The instant specification teaches only the analysis of human subjects, and does not teach the analysis of any non-human organisms.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to the quantitative analysis of RNA samples is high, the level of unpredictability in correlating any particular expression level with a diagnosis of or prediction of sepsis is even higher.

Given the breadth of the claimed method as encompassing the analysis of RNA in any mammal, it is relevant to point out that Hoshikawa et al (2003) (as cited on the IDS of 05/05/2009) teaches unpredictability with regard to applying gene expression results among different organisms. The reference teaches the analysis of gene expression in lung tissue in response to hypoxic conditions which lead to pulmonary hypertension (Fig. 1). The reference teaches that the gene expression profile in mouse is different from that observed in rat (Tables 1-4; p.209 - Abstract). Thus it is unpredictable as to whether or not the human genes disclosed in the specification of the

instant application are in fact applicable to determining the status of sepsis or SIRS in any other non-human mammal.

Because the claims encompass any compared level of RNA (any difference in RNA amounts or any changes in RNA concentration), it is relevant to point out that Cheung et al (2003) (as cited on the IDS of 05/05/2009) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) p.422, last paragraph; Fig 1). The data indicates that, for example, expression of *ACTG2* in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). It is thus unpredictable as to whether or not any level of a detected biomarker can in fact be indicative of sepsis or SIRS. This is particularly relevant where the claims generically encompass any genes or fragments (e.g. claim 1), and specifically include gene fragments with as few as 5 nucleotides of the Elected genes (e.g. claim 10). Similarly, Shalon et al (2001) (as cited on the IDS of 05/05/2009) teaches that preferably 20-50 different test individuals are assayed to obtain meaningful data showing a significant change in gene expression levels, and changes of gene expression of at least 2 fold and up to 100 fold or more are desirable for the comparison of gene expression levels between a case and control population (p.10 ¶156, ¶158).

Because the claims encompass examining RAN from any body fluid source, it is relevant to point out the unpredictability with regard to the analysis of RNA profiles

obtained from different sample types. Cobb et al (2002) teaches the analysis of gene expression in spleen and liver sample from septic mice. Notably, the reference teaches that, when compared to a non-septic sample, the relevant biomarker profiles of the septic mouse spleen and the septic mouse liver contain different biomarkers (Table 1; p.2714, middle col., lns.2-8). It is thus unpredictable as to how one might use any biomarker profile comprising biomarkers identified in a blood sample in the analysis of a biomarker profile obtained from any other body fluid.

Quantity of experimentation required

A large and prohibitive amount of experimentation would have to be performed in order to make and use the claimed invention. One would have to establish that a particular comparison (e.g. specific compared amount) of any analyzed RNA may be indicative of an individual either being septic or becoming septic. Within the scope of the claims, this would require the analysis of RNA samples from different organisms, and examining samples from different sources (e.g. blood, saliva, urine) to reliably determine the status of sepsis in the individual.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the paucity of working examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention in the full scope of the claims.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 1-9 and 11-25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 and 12-29 of copending Application No. 10/551,874. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the conflicting application are drawn to methods of diagnosing SIRS of sepsis, which would accomplish the same goal as the claims of the instant application in differentiation SIRS from sepsis.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. Claims 1-9 and 11-25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of copending Application No. 11/909,372. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the conflicting application encompass the detection of infections multiple organ failure in a subject, thus encompassing the diagnosis of sepsis in a subject which is the subject matter of the methods of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

15. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Stephen Kapushoc/
Primary Examiner, Art Unit 1634